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| EXAMINER | |
|---|---|
| RAE, CHARLESWORTH E | |
| ART UNIT | PAPER NUMBER |
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| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/726,467 | LI ET AL. | |
| | Examiner | Art Unit | |
| | Charleswort Rae | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *8,32-35 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9-31 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/04; and 1/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response Restriction/Election requirement, filed 10/19/06, is acknowledged. Applicant's information disclosure statements, filed on 1/19/05 and 3/31/04, are also acknowledged.

### Status of the Claims

Claims 1-39 are pending in this application and are the subject of the Office action.

Claims 8, 32-35, and 39 are directed to non-elected subject matter and are withdrawn from consideration for purposes of examination.

Claims 1-7, 9-31, and 36-38 are presented for examination.

### Restriction/Election

Applicant's elections of Group I, drawn to a method of administering a composition of a cell cycle checkpoint activator and an oncogenic kinase modulator, cancer species election of multiple myeloma, and composition species election of β-lapachone and imatinib, are acknowledged and made of record. Applicant's statement that claims 1-7, 9-31, and 36-38 read on the elected species is also acknowledged and made of record.

Applicant statement that s/he is reserving the right to prosecute the non-elected claims and species in a continuation or divisional application and also respectfully reserve the right to traverse the Examiner's requirement of a restriction/election in a future response is acknowledged.

It is noted that applicant's instant response fails to point out any errors in the requirement to establish a reasonable basis for traversal. Thus, applicant's election is considered to be without traverse.

**Objection to the Specification**

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention in view of applicant's provisional restriction election of invention I and species election of multiple myeloma and the combination of β-lapachone and imatinib. Applicant's cooperation is further requested in correcting this deficiency.

**Claim rejections – 112 – Second Paragraph - Indefinite**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, and 7 are rejected under 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, and 6 recite the abbreviation "Bcr-Abl," but fails to state the full meaning of the term at the first occurrence the term is recited in the claim. This limitation is vague and indefinite because it is not clear what "Bcr-Abl" means. It is suggested that this specific rejection may be overcome by either replacing the term "Bcr-Abl" with the full name or, alternatively, amend the claim by inserting the full name in parenthesis at the first occurrence of the term "Bcr-Abl" in the claim.

Claim 7 recites the abbreviation "AIDS," but fails to state the full meaning of the term at the first occurrence the term is recited in the claim. This limitation is vague and indefinite because it is not clear what "AIDS" means. It is suggested that this specific rejection may be overcome by either replacing the term "AIDS" with the full name or, alternatively, amend the claim by inserting the full name in parenthesis at the first occurrence of the term "AIDS" in the claim.

***Claim Rejections – 35 USC 112 – First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-31, 36-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating multiple myeloma and chronic myelogenous leukemia comprising administering a therapeutically effective amount of beta-lapachone in combination with imatinib or paclitaxel, does not reasonably provide enablement for methods of treating all cancers in a subject comprising administering any cell cycle checkpoint activator and any oncogenic kinase modulator. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a cell cycle checkpoint activator, and an oncogenic kinase modulator, such that the cancer is treated. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical and oncological arts are generally unpredictable, requiring each embodiment to be individually assessed for therapeutic and pharmaceutical activities. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of anticancer drugs is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. Although cancer cells proliferate rapidly, the rate of growth varies widely depending on the particular cancer cell type. This variability in the rate of growth may also affect the therapeutic responsiveness of cancer cells. Besides, there is a disproportionately sparse number of discovery of new and predictable curative cancer treatments compared with the vast number of new drugs discovered.

With respect to the state of the art, Moussa (WO 03/086497 A1) teaches a method of preventing or treating hyperproliferative vascular disease in a mammal by administering an antiproliferative effective amount of imatinib mesylate, alone or in combination with other compounds, via a vascular stent.

George et al. teach that the standard therapy for myeloma includes alkylating agents administered with prednisone (George et al. American Family Physician. 1999, vol. 59/no. 7, electronic copy, pages 1-12; see page 8, first full paragraph). George et al. also disclose that most trials have not found significant differences between combination chemotherapy and melphalan with prednisone (page 9, last full paragraph, lines 4-5).

Goodman & Gilman teach that in designing specific regimens for clinical use, a number of factors must be taken into account (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996): page 1230, third full paragraph, lines 1-2). Drugs are generally more effective in combination and may be synergistic through biochemical interactions (page 1230, third full paragraph, lines 2-3). These interactions are useful in designing new regimens (page 1230, third full paragraph, line 3). Goodman & Gilman teach that it is more effective to use drugs that do not share common mechanisms of resistance and that do not overlap in their major toxicities (page 1230, third full paragraph, lines 4-5).

2. The breadth of the claims

The claims vary in breadth; some (such as claims 1-2) vary broadly, reciting the terms "treating cancer in a subject," "cell cycle checkpoint activator," and "oncogenic kinase modulator." Cancer reasonably represents a diverse group of morphological and clinical conditions that exhibit varying degrees of therapeutic responsiveness to treatment. Claim 2 recites "β-lapachone, or a derivative or analog thereof," which necessarily encompasses a multiplicity of possible compounds which

would reasonably vary widely with respect to chemical structure/activity relationships, pharmacologic/pharmaceutical/therapeutic effects. Other claims, such as claims 18, 37, and 38 are narrower, reciting "beta-lapachone" and "imatinib". All, however, are extremely broad insofar as they disclose a method of treating cancer in a subject. Also, claim 2 encompasses derivatives and analogs of β-lapachone which reasonably may exhibit wide variability with respect to chemical/ pharmacologic/ therapeutic properties. Thus, the level of predictably in practicing the claimed invention would be greatly diminished in view of the fact that the therapeutic response to be achieved with the instant method would reasonably vary widely depending upon the type of cancer being treated and the specific chemical/therapeutic agent or combination of therapeutic agents that are used to practice the instant method.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides limited direction or guidance for determining the particular administration regimens (dosages, timing, administration routes etc.) necessary to treat all cancers comprising administering any checkpoint activator and any oncogenic kinase modulator. The 'working examples" are limited to multiple myeloma and chronic myelogenous leukemia, and the therapeutic combination comprising beta-lapachone and imatinib. Figure 1A shows the effect of combined treatment with β-lapachone and imatinib on human multiple myeloma cells (see also specification, page 5, lines3 1-33); Figure 1B shows the effect of treatment with β-lapachone or imatinib on human multiple myeloma cells (see also specification, page;

Figure 6, lines 1-2); Figure 2A shows the effect of treatment with β-lapachone or imatinib on human chronic myelogenous leukemia cell lines; and Figure 2C shows the effect of combined treatment with β-lapachone and imatinib on human chronic myelogenous leukemia cell lines. Also, Table 1 (specification, page 10-11) and Table 2 (specification, page 11) disclose general examples of therapeutic agents and their mechanism of action. However, there is no structure-activity data disclosed to reasonably predict the therapeutic effects to be achieved when the listed agents are practiced by the instant treatment method. Thus, the applicant at best has provided specific direction or guidance only for a general administration protocol for treatment of cancers.

4. The quantity of experimentation necessary

In view of applicant's unexpected results achieved with the instant invention as exemplified in figures (1A, 1B, 2A, and 2B), it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention in all cancer patients. Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for any cancer.

For the reasons stated above, claims 1-7, 9-31, 36-38 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

**Claim rejections – 112 – First Paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:**

Claims 1-7, 9-31, and 36-38, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses specific cell cycle checkpoint activators, including β-lapachone, and specific oncogenic kinase modulators, including imatinib, which meet the written description and enablement provisions of 35 USC 112, first paragraph (see specification, page 10, line 25 to page 14, line 1; Tables 1 & 2). For example, instant claims 36-38, are directed to encompass "derivatives or analogs" which only correspond in some undefined way to specifically instantly disclosed chemicals. For example, instant claim 1 is directed towards any cell cycle checkpoint activator and any oncogenic kinase modulator, but the specification does not provide any specific disclosure with respect to the relationships between the common functional feature of the genus, and the diverse chemical features, and/or the diverse group of cancers encompassed by the claims, and/or the contemplated therapeutic effect to be achieved

in practicing the instant invention. Thus, none of the "derivatives or analogs," or undisclosed oncogenic kinase modulator/cell cycle checkpoint activator, compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are, and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision.

**Claim rejections – 35 USC 103(a)**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9-18, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardee et al. (U.S. Patent 7,070,797), in view of Topay et al. (Topay et al. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor ST1571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. Leukemia (2001), 15:342-347, **electronic copy pages 1-13**).

Pardee et al. teach methods for treating human multiple myeloma by administering a G1 and/or S phase drug, in a therapeutically effective amount (column 3, line 39 to column 4, line 3). Pardee et al. teach that the major check points occur at G1/S phase and at the G2/M phase transitions where cells make a commitment to repair DNA or undergo apoptosis (column 2, lines 63-65). In one embodiment, the method comprises administering a combination of a G2/M phase drug and a G1 and/or S phase drug for the treatment of MM and other hematologic tumors and/or malignancies (column 3, lines 44-49). In another embodiment, the method comprises administering a combination of β-lapachone and paclitaxel (Taxol) (column 7, lines 1-3). In particular, claim 1 of the reference is directed to a method of treating multiple myeloma in a subject comprising administering to the subject a therapeutically effective amount of beta-lapachone, or a derivative or analog thereof. Pardee et al. disclose pharmaceutical compositions comprising the combination therapies in dosage forms as a solid, semi-solid, or liquid; the compositions may also include, depending on the formulation desired, pharmaceutically-acceptable, nontoxic carriers or diluents (column 15, lines 6-40). The combination therapy agents may be administered singly and sequentially, or in a cocktail or combination containing both agents, including but not

limited to, immunosuppressive agents, potentiators and side-effect relieving agents (column 14, lines 61-67). The therapeutic combinations are preferably administered intravenously or otherwise systemically by injection intramuscularly, subcutaneously, intrathecally or intraperitoneally (column 15, lines 2-5). The compounds can be administered by any means known in the art, including oral, rectal, nasal, topical, buccal and sublingual (column 16, lines 1-7). Pardee et al. also teach that the combination of the present invention (i.e. the combination a G1/S phase agent and a G2/M phase agent) results in a surprising synergy which is beneficial in reducing tumor burden load and/or regressing tumor growth, especially in patients with metastatic disease (column 9, lines 3-6). Pardee et al. do not teach imitanib as practiced by the instant method of treating multiple myeloma.

Topay et al. disclose that imatinib (or ST15171) exhibits strong synergism with apoptosis-inducing when used in combination with other chemotherapeutic drugs to treat BCR-ABL-positive cells *in vitro* (Topay et al. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor ST1571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. Leukemia (2001), 15:342-347, **electronic copy pages 1-13;** see electronic page 9, first full paragraph, lines 1-9).

Based on the synergistic effects of the combination of beta-lapachone and paclitaxel as disclosed by Pardee et al., someone of skill in the art would have been motivated to combine the teaching of Pardee et al. and Topay et al. by substituting the paclitaxel (.ie. G2/M phase agent) with another G2/M phase agent, for example, imatinib, to create the instant method (column 7, lines 1-15).

Thus, for the reasons stated above, someone skilled in the art would have deemed it obvious to create the instant inventive concept in view of the teachings teaching of Pardee et al., in view of Topay et al. to arrive at the instant inventive concept with a reasonable expectation of success.

**Claim rejections – 35 USC 103(a)**

Claims 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardee et al. (U.S. Patent 7,070,797; hereafter referred to as Pardee '797), in view of Topay et al. (Topay et al. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor ST1571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. Leukemia (2001), 15:342-347, **electronic copy pages 1-13**), further in view of Pardee AB, et al. (U.S. Patent 6,664,288), and further in view of Lyons et al. (U.S. Patent 6,998,391).

The above discussions of Pardee '797 and Topay et al. are incorporated by reference.

Pardee et al. (Pardee '288) teach a composition and a method for treating cancers in mammals comprising the administration of a compound that targets cells at G1 and/or S phase, such as a topoisomerase I inhibitor e.g. beta-lapachone, in combination with a compound that targets cells at the G2/M phase e.g. paclitaxel (column 2, lines 47-52). Pardee et al. further disclose that no single drug or drug combination is curative for advanced metastatic cancers and patients typically succumb to the cancers in several years, such that new drugs or combinations can prolong onset

of life-threatening tumors and/or improve quality of life by further reducing tumor-load (column 2, lines 26-31). Table 1 of the reference discloses a list of drugs, and their mechanism of actions, that are encompassed by the invention (column 4). Pardee et al. teach that in administering the compounds one can use the normal dose of each compound individually, but lower doses are preferred (column 8, lines 13-17). Pardee et al. also disclose that the compounds can be administered by any means known in the art (column 8, lines 1-12). In one embodiment, beta-lapachone and paclitaxel were used in combination for determination of the synergistic effects of the combination(column 16, lines 44-58). Synergism was schedule dependent and was observed only if paclitaxel was added after beta-lapachone treatment (column 16, lines 53-58). The combination of beta-lapachone and paclitaxel dramatically reduced cell survival in a variety of human cancer cells, including ovarian, breast, prostate, melanoma, lung, and pancreatic cancer cell lines (column 16, lines 59-66). In particular, claim 1 of the reference is directed towards a method of treating a mammal having a solid tumor (or tumors) formed as a result of a cancer selected from, the group consisting of melanoma, colon cancer, prostate cancer, lung cancer, pancreatic cancer, ovarian cancer, and breast cancer, the method comprising

a) administering to the mammal an effective amount of a first compound comprising beta-lapachone or derivatives thereof as the active ingredient; and

b) administering to the mammal an effective amount of a G2/M phase drug.

The reference does not teach combination comprising beta-lapachone and imatinib combination therapy, however.

Lyons et al. teach compositions, kits, and methods for treating a host, preferably human, having or predisposed to a disease associated with abnormal activity of protein kinase (column 2, lines 44-47). In one embodiment, the method comprises administering to a patient having chronic myelogenous leukemia imatinib mesylate and a DNA methylation inhibitor (column 3, lines 13-15). Lyons et al. disclose that imatinib may be given to the patient in a dose of 100-800 mg/day, which may optionally last for a period of at least 2, 4, 6, 8, 10, or more days (column 4, lines 27-32).

Li et al. has been made of record by applicant and is cited to show the general state of the art. (Li et al. Potent inhibition of tumor survival in vivo by β-lapachone plus Taxol: combining drugs imposes different artificial checkpoints. PNAS (1999), vol. 96(23): 13369-13374). Li et al. teach that preliminary experiments involving the combination of beta-lapachone and Taxol produced dramatic antitumor activity against xenografted human prostate cancer, which suggests a combination chemotherapy of very great effectiveness as wells as a potential avenue for developing anticancer therapies (page 13369, column 1, firs full paragraph).

Based on the disclosure of Pardee et al. ('797) that the combination of beta-lapachone and paclitaxel results in synergistic effects, someone of skill in the art would have been motivated to combine the teaching of Pardee et al. ('797), in view of Topay et al., in further view of Pardee et al. ('288), and further in view of Lyons et al. to create the instant invention.

Thus, for the reasons stated above, someone skilled in the art would have deemed it obvious to create the instant inventive concept in view of the teachings

teaching of Pardee '797, in view of Topay et al., in view of Pardee '288, and further in view of Lyons et al. to arrive at the instant inventive concept with a reasonable expectation of success.

***Nonstatutory Obviousness-Type Double-Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 7, 9-21, 23-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 3-13, 15-40, 42, 45-48, 50-51 of U.S. Patent 7,070,797 (Pardee '797), in view of Topay et al., in further view of Pardee et al. ('288), and further in view of Lyons et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

The above discussions of Pardee '797, Topay et al., Pardee '288, and Lyons et al. are incorporated by reference. Based on the synergistic effects of the combination of beta-lapachone and paclitaxel as disclosed by Pardee et al., someone of skill in the art would have been motivated to combine the teaching of Pardee et al. and Topay et al. by substituting the paclitaxel (.ie. G2/M phase agent) with another G2/M phase agent, for example, imatinib, to create the instant method (column 7, lines 1-15).

To reiterate, Pardee '797 does not teach the instant combination of beta-lapachone and imatinib. Except for imatinib, the instant claims overlap with the reference claims. For example, claim 1 of Pardee '797 is directed towards a method of treating multiple myeloma in a subject comprising the administering to the subject a

therapeutically effective amount of beta-lapachone, or a derivative or analog thereof. To the extent that reference claim 1 recites the transitional phrase "comprising," it is reasonably envisioned that additional treatment steps are contemplated. Thus, someone of skill in the art at the time the instant invention was made would have deemed it obvious to create the instant claimed invention with a reasonable expectation of success in view of the teaching of Pardee '797, in view of Topay et al., in view of Pardee '288, and further in view of Lyons et al.

Claims 1-7, 9-31, and 38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent 6,664,288 (Pardee '288), in view of Pardee '797, in view of Topay et al., and further in view of Lyons et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

The above discussions of Pardee '288, Pardee '797, Topay et al., and Lyons et al. are incorporated by reference.

In particular, claim 1 of Pardee '288 is directed towards a method of treating a mammal having a solid tumor selected from a group consisting of melanoma, colon cancer, prostate cancer, lung cancer, pancreatic cancer, ovarian cancer and breast cancer, comprising administering an effective amount beta-lapachone or derivatives thereof and an effective amount of a G2/M phase drug. Pardee '288 does not specifically teach imatinib. However, the recitation of the transitional phrase "comprising" in the instant methods reasonably contemplate additional method steps.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant inventive concept with a reasonable expectation of success in view of the teaching of Pardee '288, in view of Pardee '797, in view of Topay et al., and further in view of Lyons et al.

Claims 1-7, 9-31, and 36-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-26, 30-31, 34-38, 40-46, 50-51, 55-58, 60-64, 94-95, 101-105, 107-111 of copending US Patent Application No. 10,007,352, and claims 1-24, and 26-41 of copending US Patent Application No. 10,846,980. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the copending applications are directed towards treating cancer by administering a G1 and/or S phase of the cell cycle, preferably beta-lapachone with a drug that modulates the G2/M phase of the cell cycle i.e. imatinib.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 8 a.m. to 4:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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19 March 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER